Salvage of renal allograft function and lower extremity venous patency with thrombolytic therapy: Case report and review of the literature

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Five months after a cadaveric renal transplant a 69-year-old man was admitted with caval, iliac, and renal allograft vein thrombosis that occurred in the setting of a previously placed caval filter. The patient's urine output and renal function deteriorated rapidly. Thrombolytic therapy with urokinase was begun, and lysis of the thrombus occurred in 72 hours. The patient's renal function returned to baseline, and the transplant was salvaged. Moreover lower extremity venous patency and valvular function were maintained. We report the case and review the literature on thrombolytic therapy for renal allograft vein and lower extremity deep venous thrombosis. (J VASC SURG 1995;21:691-6.)

Renal allograft vein thrombosis occurs in a small percentage of renal transplant recipients but in the past has often resulted in loss of the transplant.[1-3] Restoration of allograft venous flow has most frequently been attempted surgically.[1] In this article we report the use of thrombolytic therapy for the treatment of iliac, femoral, and allograft vein thrombosis. This treatment resulted in salvage of renal allograft function. Moreover short-term venous patency and valvular function were maintained.

CASE REPORT

A 69-year-old white man was admitted for mental status changes and hypoxia. Five months previously the patient had undergone cadaveric kidney transplantation for end-stage renal disease caused by hypertension. Anastomosis was performed on the renal allograft artery and vein in an end-to-side fashion to the left external iliac artery and vein, respectively. Two months before he was admitted, the patient had development of a left femoral deep venous thrombosis complicated by a pulmonary embolus. Initial treatment for the venous thromboembolic disease consisted of heparin sodium followed by warfarin anticoagulation. However, 1 month before this admission the patient reported severe lumbosacral pain, and workup demonstrated degenerative spinal disease. The anticoagulation was discontinued in anticipation of lumbar laminectomy, and a titanium Greenfield filter was placed in the infrarenal vena cava via a percutaneous right femoral approach.

Physical examination at admission was remarkable for severe hypotension, obtundation, exquisite tenderness and fullness over the renal allograft, and abdominal distention. The lower abdomen and pelvis had cyanotic mottling that became confluent over both legs. The feet were cold and deeply cyanotic. Arterial oxygen saturation on 100% nonrebreather mask was 80%, and marked hemoconcentration was present with the hematocrit increased to 55% from a known baseline of 31%. The patient had anuria and a small amount of blood in the bladder drainage catheter. The serum creatinine level was elevated to 2.4 mg/dl from a baseline of 1.6 mg/dl and continued to rise at an anephric rate. Supportive measures resulted in normalization of the arterial blood pressure with no change in the appearance of the lower extremities or urine output. Because Doppler-derived pedal arterial pressures were normal, a clinical diagnosis of phlegmasia cerulea dolens and transplant renal vein thrombosis was made. Color flow duplex ultrasonography of the left iliac fossa renal allograft demonstrated decreased arterial diastolic flow, absent venous flow, and marked allograft enlargement. The external and common iliac veins bilaterally and the proximal left common femoral vein were thrombosed, and thrombus extended proximally in the inferior vena cava to the level of the Greenfield filter. Twenty thousand units of heparin sodium were administered.

Emergency iliac and caval venography via a left femoral approach demonstrated occlusive thrombus extending from the proximal left common femoral vein to the inferior

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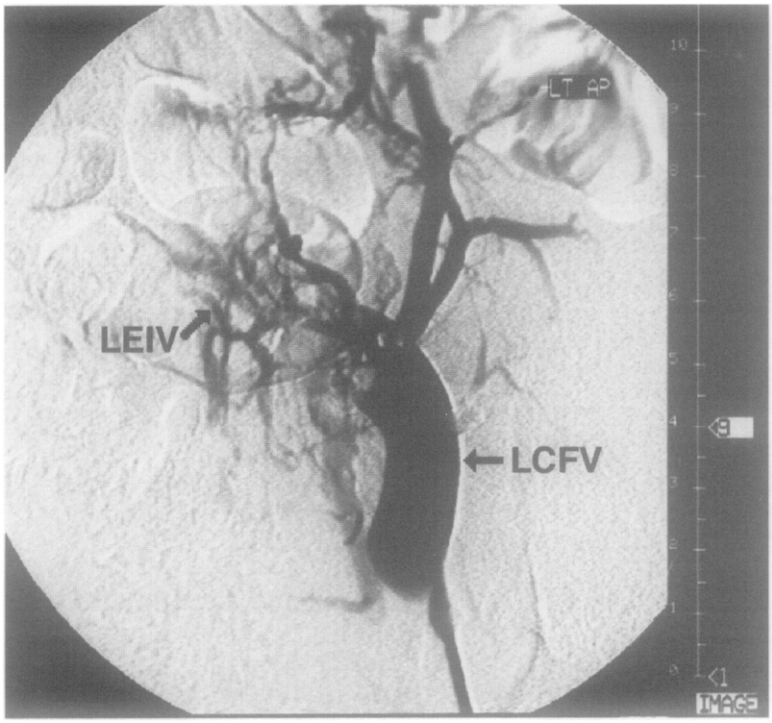

Fig. 1. Venograph demonstrating thrombosis of left *(LEIV)* external iliac vein. Left common femoral vein *(LCFV)* is patent. Renal allograft vein is not visualized.

vena cava at the level of the Greenfield filter. The renal allograft vein was not visualized (Figs. 1 and 2). Simultaneous pressure measurements in the transplant renal vein and the vena cava above the Greenfield filter were 50 and 8 mm Hg, respectively. With the use of the left femoral approach a catheter with multiple side holes was positioned from the common femoral vein to the caval filter, and urokinase infusion was begun at a rate of 240,000 U/hr. This infusion was continued for 4 hours and was then decreased to 100,000 U/hr overnight. The patient was also given 2500 U heparin sodium per hour, and the partial thromboplastin time was kept between 90 to 120 seconds. The fibrinogen level was monitored and remained between 100 and 400 mg/dl throughout the infusion.

Twenty-four hours after thrombolytic therapy was initiated, the patient remained anuric. The left foot was markedly improved, but the right foot was essentially unchanged. Venography revealed partial resolution of the left femoral, iliac, and caval thrombus (Fig. 3). The renal allograft vein pressure was equal to the systemic venous pressure. A second side hole catheter was placed into the thrombosed right iliac vein. Urokinase was infused through the left-sided catheter at 60,000 U/hr and through the right-sided catheter at 120,000 U/hr. Complete resolution of the lower extremity cyanosis was present by the next day. The urokinase was discontinued, and the patient was given sufficient systemic heparin sodium to maintain the partial thromboplastin time between 80 and 100 seconds. For the next 5 days the urine output gradually increased to polyuric levels and then normalized. The serum creatinine level peaked at 5.9 mg/dl before returning to a baseline of 1.2 mg/dl. Repeat renal duplex scanning on the fifth hospital day demonstrated patency of the transplant renal artery and vein, the femoral and iliac veins bilaterally, and the inferior vena cava. Renal allograft swelling had improved as had the parenchymal arterial diastolic flow. Subsequent evaluation of fever, headache, and backache revealed *Cryptococcus neoformans* meningitis and fungemia. Resolution of this infection was achieved with a 6-week course of amphotericin B. Anticoagulation was continued for approximately 30 days, until the patient had upper gastrointestinal bleeding that required transfusion of 4 units of blood; at this time the anticoagulation was discontinued. The patient was discharged on the seventy-fifth hospital day and was prescribed 325 mg aspirin daily. After 4 months he has no symptoms and is ambulatory. Repeat duplex scanning has demonstrated continued patency of all deep veins and competent lower extremity venous valves.

DISCUSSION

Renal allograft vein thrombosis is an unusual cause of allograft dysfunction. Previous studies have documented an incidence of 1% to 4%.[1,2] However, in most cases it has led to loss of the allograft. The

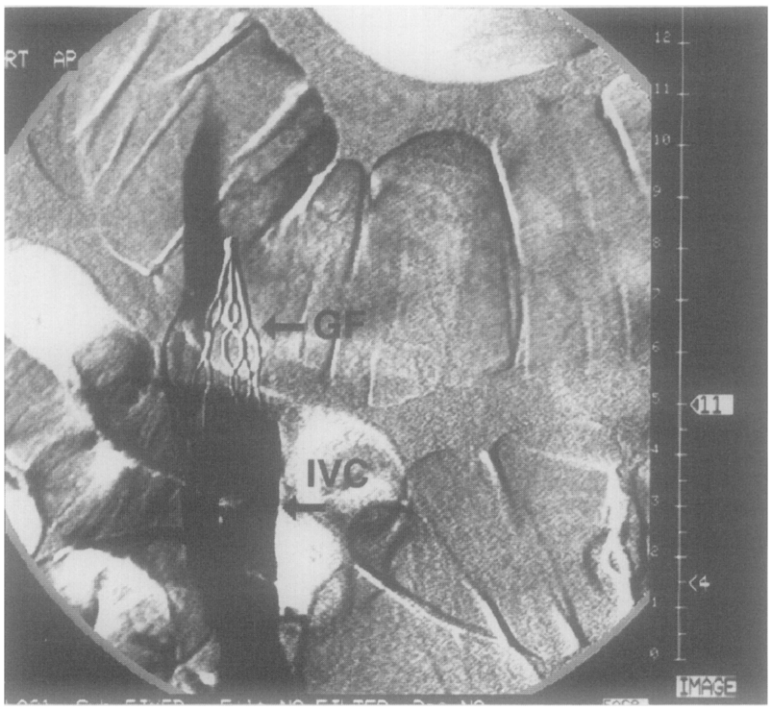

Fig. 2. Venograph demonstrating thrombus in inferior vena cava *(IVC)* at level of Greenfield filter *(GF)*.

most common time of occurrence is in the early posttransplant period and is attributed to kinking of the vein in the iliac fossa, external compression from a hematoma, lymphocele, or abscess, use of multiple artery or pediatric kidneys, or rejection.[3] Late thrombosis is attributed to rejection, glomerulonephritis, or extension of lower extremity deep venous thrombosis.[1]

Treatment of renal allograft vein thrombosis has traditionally been surgical, but the results have been disappointing. In most cases the graft was lost, and in many it was nonviable at the time of exploration.[4] The increased availability and success of thrombolytic therapy has led to its use for the treatment of renal allograft vein thrombosis. Five case reports have been published in which patients underwent successful thrombolysis and restoration of renal function with streptokinase or urokinase.[5-9] The presentation of the patient in most cases was nonspecific and was suggestive of rejection with allograft tenderness, decreased urine output, and elevated creatinine. In two of the five cases[7,8] lower extremity edema suggesting the presence of deep venous thrombosis was present. Two patients had histories of lower extremity deep venous thrombosis.[5,8]

Diagnosis in the published reports was made by duplex ultrasonography or venography. The duplex scan demonstrates absence of venous flow and changes in the arterial flow pattern including abruptly decreasing systolic frequency shifts and retrograde plateaulike shifts during diastole. It has the advantage of not requiring intravenous contrast, which can be harmful to renal function. Venography, however, remains the gold standard and is necessary to direct lytic therapy.

In the previously published reports thrombolytic therapy was infused via the renal allograft artery in two cases,[6,9] the renal allograft vein in two cases,[5,8] and via both vessels in one case.[7] Catheter location did not affect the success of thrombolysis or the rate. In all reported cases[5-9] and, in our case, patients experienced decreased urine output and renal function associated with allograft vein thrombosis. After lytic therapy was initiated, radiologic progression of lysis paralleled increasing urine output. However, recovery of renal function as demonstrated by decreasing creatinine lagged lysis by several days. In the case of our patient 48 hours after lytic therapy was begun, most of the thrombus was gone, and the urine output averaged 150 cc/hr. The creatinine concentration, however, continued to rise for 3 additional days, reaching a peak of 5.9 mg/dl. It returned to baseline approximately 1 week later.

Lytic therapy for renal allograft vein thrombosis

Fig. 3. Venograph demonstrating partial resolution of left external iliac *(LEIV)* thrombus. Left common femoral and common iliac veins are patent.

appears to be efficacious in cases where it results from accompanying deep venous thrombosis. Clearly in cases of compression by lymphocele or hematoma or kinking of the allograft vessels, a radiologic or surgical procedure would also be required to maintain venous patency. Moreover, early diagnosis and emergent therapy is essential to preserve renal function.

The mechanism of caval thrombosis in this case is not clear. Caval thrombosis from titanium Greenfield filters occurs in only 5% of patients. Preliminary results of a long-term study currently in progress in our laboratory have demonstrated an incidence of 2% at 2 years. Deep venous thrombosis with proximal progression of thrombus at the insertion site is also unusual, occurring in approximately 6% of patients.[10] Laboratory data have failed to demonstrate any abnormalities of antithrombin III, protein C, or protein S in this patient. The most likely mechanism of thrombosis may have been embolic occlusion of the filter with subsequent iliac and femoral thrombosis. In this case it is also noteworthy that the episode of fungal sepsis was treated successfully without infection of the filter. Previous studies have documented the resistance to infection of Greenfield filters in the setting of bacteremia.[10]

Rapid lysis of the caval, iliac, and femoral thrombus in this patient resulted in preservation of a patent lower extremity venous system 4 months later. Color flow duplex scanning demonstrated complete recanalization of the deep venous thrombosis and preservation of venous valvular function. In the past the use of thrombolytic therapy for venous thromboembolic disease has been controversial. A number of studies evaluating its short-term efficacy by comparing pretreatment and posttreatment venography have been published.[11-19] The studies are difficult to interpret because of small size, inadequacy of randomization and blinding, and different treatment regimens. Nevertheless, taken together they suggest that more lysis occurred in groups of patients who received lytic therapy with streptokinase than in those who received heparin only.[20] A compilation of the results of nine randomized studies including 297 patients divided into those who received streptokinase plus anticoagulation and those who received anticoagulation alone found similar results. Sixty-one percent of the patients who received streptokinase demonstrated some improvement on posttreatment venography, and 45% showed substantial improvement. In contrast, only 25% of patients treated with anticoagulation alone demonstrated any improve-

ment, and only 5% demonstrated substantial improvement.[20]

The long-term benefit of thrombolytic therapy in the treatment of deep venous thrombosis is less well proven. Ideally rapid lysis of thrombus should preserve venous valvular function. This function in turn should prevent the development of the postthrombotic syndrome and its debilitating symptoms of lower extremity pain, edema, and ulceration. Unfortunately, it has been difficult to demonstrate a benefit of thrombolytic therapy in preventing the development of chronic venous insufficiency. Studies assessing the long-term benefit have been published,[16,18,19,21-24] but they are small, uncontrolled, and have produced conflicting results. Moreover, the follow-up periods are usually too short to allow for full development of chronic venous insufficiency in all patients. In one study of streptokinase treatment,[25] patients with residual thrombus were more likely to have symptoms of chronic venous insufficiency than were those with early complete lysis. However, a study of 153 patients evaluated prospectively for 2 years after treatment with streptokinase or heparin showed no difference in clinical or hemodynamic measurements of chronic venous insufficiency in either group.[26]

Our patient initially experienced a limited deep venous thrombosis in the common femoral vein, which was treated only with anticoagulation. The episode described in this report, treated with lytic therapy, was much more extensive. Four months after the second episode our patient's venous system remains patent with normal valvular function by duplex scanning. It is clearly too early to tell whether he will have chronic venous insufficiency, but our initial findings are promising. In a previous study,[27] valvular incompetence was present 3 months after development of acute deep venous thrombosis. Moreover, although anticoagulation during his initial limited episode of thrombosis may have been effective in preventing valvular incompetence, it is unlikely to have been successful in preventing destruction of valves associated with the much more extensive thrombosis that developed the second time. Studies have also demonstrated that valve destruction most often occurs in areas that have previously been thrombosed,[27,28] suggesting that it results from direct injury to the valves by the thrombus. Although lytic therapy might not be beneficial in limited deep venous thrombosis, it may be helpful in preserving valvular function in extensive cases, if initiated early.

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